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EXAMINER: JONES, E

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-31 is/are pending in the application.

Of the above, claim(s) 1-25, 28-31 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 26-27 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Part III DETAILED ACTION

Applicant's election without traverse of claims 26 and 27 in Paper No. 10 is acknowledged.

Claims 1-25 and 28-31 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 10.

The drawings filed on 06/07/95 are objected to by the Draftsperson under 37 CFR 1.84 (b).

Photographs are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their formal use. In the event applicant wishes to use the photographs currently on file, a petition must be filed for acceptance of the photographs. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(h) and three sets of drawings or photographs, as appropriate.

Claim Rejections - 35 USC § 112 1st **Paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and use the invention.

The claims of the instant invention are broad in that they encompass all neural stem cell progeny and it is not apparent from the specification that any and all neural stem cell progeny can be obtained and transplanted as claimed. Also, the claims are broad in that they read on any transplantation site and it is not clear form the specification that these cells could be transplanted to any site within an organism.

The claims of the instant invention are drawn to a method of transplanting neural stem cells progeny to a host, wherein the neural stem cell progeny are first cultured in a medium containing at least one proliferation inducing growth factor capable of producing progeny of neural stem cells and transplanting the neural stem cell progeny into a host. The instant invention is also drawn to a method of transplanting neural stem cells progeny to a host, wherein the neural stem cell progeny are genetically modified to express a biological agent including, growth factors, growth factor receptors, neurotransmitters, neurotransmitter synthesizing genes, neuropeptides, and chromaffin granule amine transporter.

The specification of the instant application discloses on page 17 that the claimed invention is directed towards a method for treating neurodegenerative diseases. The specification, however, provides no examples that demonstrate that the transplantation of any neural stem cell produces any therapeutic effect for the treatment of neurodegenerative diseases in any organism. The specification on pages 67 and 68 states that neural stem cell progeny are injected into humans and that neurological evaluations can be performed, however, no data regarding any therapeutic effect is given. Example 15 on pages 68-70, shows that transplanted neural stem cell progeny proliferated in vitro were transplanted into rats and upon removal of the spinal cords, patches of myelin were noticed, however, it is not clear that the results from this experiment are indicative of any therapeutic effect. Example 45, beginning at page 96 of the specification demonstrates that neural stem cells(NSC) derived from rat transgenic to express β-galactosidase, Rosa 26 cells and human NSCs were transplanted into the CNS of rats. Results demonstrated the presence of β-gal or the presence of BrdU (incorporated during in vitro culture) in neural tissue upon animal sacrifice, however, the specification does not specifically state the amount of time that passed in between the time when the cells transplanted and the time of analysis.

The specification has demonstrated methods for producing, culturing and transplanting neural stem cells, however, the

specification has not demonstrated that the claimed invention is enabled for the treatment of neurodegenerative diseases. None of the examples provided in the specification demonstrate that a therapeutic result was achieved for the treatment of any neurodegenerative disease. Furthermore the specification and the prior art lack guidance on several parameters involving the transplantation of neural stem cell progeny to effect therapy for the treatment of neurodegenerative diseases, which would be required for the skilled artisan to practice the invention. The specification does not disclose amounts of cells to be administered, what amount of cells are required to achieve a therapeutic effect, sites for transplantation, requirements for repetitive transplantation and ways of measuring that a therapeutic effect has been achieved. The specification also lacks working examples that demonstrate that any neural stem cell progeny transplanted can effect a therapeutic result. It is also not apparent that genetically altered cells would deliver any gene product in vivo that would be expressed at a level adequate to achieve a therapeutic result. Furthermore the art regards the treatment of neurodegenerative diseases using cell grafts as unpredictable. Emerich (Cell Transplantation) discloses that the treatment of neurodegenerative disorders is unpredictable and that neural transplants do not necessarily produce behavioral recovery and in some cases have either no beneficial effects, magnify existing behavioral abnormalities or even produce a

unique constellation of deficits. Although Emerich is discussing transplantation of fetal neural tissue, the same arguments may be made when using genetically engineered cells to produce the neural factors. Emerich further discloses neurodegenerative diseases produce unique patterns of behavioral symptoms which are associated with the destruction of specific neuronal populations and that while we are gaining an understanding of the pathology and molecular biology of these disorders, there remains a wide gap between our understanding of the neural substrates of these disorders and our ability to effectively prevent or treat them. Emerich discloses that for example, regarding Parkinson's Disease, the current pharmacological strategy on increasing the striatal dopamine levels by administration of L-dopa has met with limited long term success and may even result in deleterious side effects. Emerich discloses that the extent of functional recovery in the animal models depended on the location of the transplanted tissue and the subsequent compartmentalization of dopamine release.

Claim 27 reads on ex vivo gene therapy, in which the level of skill in this art is very high, however, still remains very unpredictable, as exemplified by Orkin et al. which states:

> 2. "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols".
> 3. "Significant problems remain in all basic aspects of gene therapy".

Applicant is also directed to Friedmann et al. which discloses the state of gene therapy for neurological disorders at about the time the invention was made, and states:

> The gene therapy tools currently in use are blunt, and will remain so until solutions are found to the technical problems posed by the need for persistent transgene expression, specific targeting of foreign genes to the appropriate tissues, site specific integration of retro viral vectors and adeno associated vectors, stable gene transfer into post-mitotic cells, and also by the need to overcome the immune response to the gene transfer vector and the transience of gene expression from non integrating vectors. These issues are relevant to gene therapy applications in all organs, including the CNS.

In view of the lack of guidance presented above, correlatable in vivo working examples, level of skill in the art, unpredictability in the art, nature of the invention, and the breadth of the claims, undue experimentation would be require of one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 26 is rejected under 35 U.S.C. § 102(a) as being anticipated by Lubetzki et al. [Annals of the New York Academy of Sciences, (1990) vol 605:66-70].

Lubetzki et al. teach a method of transplanting neural stem cell progeny. Nerve stem cell cultures are obtained from rat brains and expanded using PDGF. Oligodendrocyte precursors were

then purified and expanded in culture. These cells were then transplanted into the thalamus of rats by injection .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

1. Claims 1-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Lubetzki et al. [Annals of the New York Academy of Sciences, (1990) vol 605:66-70] in view of Gage et al. [U.S. patent 5,082,670]..

Lubetzki et al. teach a method of transplanting genetically engineered O-2A into the brains of rats. Nerve cell cultures are obtained from rat brains and expanded using PDGF. Oligodendrocyte precursors were then purified and transfected in vitro with retrovirus and phosphocalcium precipitation to express the Lac-z gene. These cells were then injected into the thalamus of rats. The animals were then sacrificed and analyzed for the

Lac-z expression. This reference differs from the claimed invention in that the neural stem cell progeny are transduced to express a marker gene and not a biological agent selected from a group consisting of growth factors, growth factor receptors, neurotransmitters, neurotransmitter synthesizing genes, neuropeptides, and chromaffin granule amine transporter.

Gage et al., however, teaches methods of transplanting genetically altered cells to treat diseased or damaged cell within the CNS. Gage et al. teaches at column 12 that several types of cells can be genetically altered and transplanted into the CNS including embryonic neuronal cells replicating adult neuronal cells and reactive glial cells, and suggests the use of other mammalian cells suitable for genetic manipulation. Gage et al. teaches the transplantation of cells genetically modified to express NGF and L-DOPA. One skilled in the art would expect that the cells taught by Lubetzki et al. could be substituted for any of the cells as taught by Gage et al. to express either NGF and L-DOPA as taught by Gage et al. for purposes of transplantation, especially absent any evidence of the contrary. Thus is would have been obvious to the skilled artisan to substitute neural stem cell progeny cells as taught by Lubetzki et al. for any of the cells as taught by Gage et al. such that the neural stem cell progeny would be genetically modified to express a growth factor or a neurotransmitter synthesizing gene such as tyrosine hydroxylase as taught by Gage et al. Thus, the invention as a

whole would have been obvious to the skilled artisan at or about the time the invention was made, especially lacking evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernest Jones whose telephone number is (703) 305-7018. In the event that the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at (703) 308-3153. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ernest Jones

December 12, 1996.

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800